Bortezomib Augments Natural Killer Cell Targeting of Stem-Like Tumor Cells.

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Public Summary:
Tumor cells harboring stem-like/cancer stem cell (CSC) properties have been identified and isolated from numerous hematological and solid malignancies. These stem-like tumor cells can persist following conventional cytoreductive therapies, such as chemotherapy and radiotherapy, thereby repopulating the tumor and seeding relapse and/or metastasis. We have previously shown that natural killer (NK) cells preferentially target stem-like tumor cells via non- major histocompatibility complex (MHC) restricted mechanisms. Here, we demonstrated that the proteasome inhibitor, bortezomib, augments NK cell targeting of stem cell-like tumor cells against multiple solid human tumor-derived cancer lines and primary tissue samples. Mechanistically, this was mediated by the upregulation of cell surface NK ligands MHC class I chain-related protein A and B (MICA and MICB) on aldehyde dehydrogenases (ALDH)-positive CSCs. The increased expression of MICA and MICB on CSC targets thereby enhanced NK cell mediated killing in vitro and ex vivo from both human primary tumor and patient-derived xenograft samples. In vivo, the combination of bortezomib and allogeneic NK cell adoptive transfer in immunodeficient mice led to increased elimination of CSCs as well as tumor growth delay of orthotopic glioblastoma tumors. Taken together, our data support the combination bortezomib and NK transfer as a strategy for both CSC targeting and potentially improved outcomes in clinical cancer patients.

Scientific Abstract:
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